UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/494,751	01/31/2000	Bernard Rees Smith	0769.00136	3862

23552 7590 08/12/2003

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
DO, PENSEE T

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/12/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/494,751	SMITH ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-90* is/are pending in the application.

4a) Of the above claim(s) *63-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response Entry & Claim Status

The response filed on May 19, 2003 has been acknowledged and entered. Claims 77-90 are pending. Claims 63-76 are non-elected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention: - the instant invention is directed to a kit for screening autoantibodies to thyroid stimulating hormone receptor (TSHR) or at least a

TSHR fragment which kit comprises a source of TSHR or a TSHR fragment, said TSHR or TSHR fragment each having at least a first and second distinct epitope regions, wherein autoantibodies to said TSHR or TSHR fragment bind to the first epitope region but not said second epitope region; at least one antibody or fragment thereof, that binds to said second epitope region of the TSHR or TSHR fragment.

The state of the art: - the prior art fails to teach a kit comprising a TSHR or a TSHR fragment comprising THS receptor fragment wherein autoantibodies to said TSHR fragment bind to the first epitope region but not second epitope region.

The predictability or lack thereof in the art:- in view of the lack of teachings in the prior art that show or suggests TSHR or TSHR fragment that have epitopes that are recognized by autoantibodies. The teaching in the specification, example 4, that the last sixty amino acids of the TSHR encoded by cDNA base pairs 1809-2295 was employed in the fusion protein because it represents a region of the TSHR that is almost entirely intracellular (within the cell) and thus not likely to interact with the TSHR autoantibodies present in the circulation is contrary to the requirement of the claimed invention- the THSR is recognized by the autoantibodies.

The amount of direction or guidance present: - the instant specification fails to provide guidance on how the TSHR which has an intracellular region would be recognized by the autoantibodies.

The presence or absence of working examples:- there is no examples in the specification that show the intracellular region of the TSHR which would be recognized by autoantibodies.

The quantity of experimentation necessary: - it would require an undue amount of experimentation for a skilled artisan to make and use the invention as claimed.

The relative skill of those in the art: The level of skill in the art is high.

The breadth of the claims:- the claimed kit is directed to a TSHR or TSHR fragment comprising two distinct epitope regions wherein autoantibodies bind to the first epitope region and at least one antibody or fragment thereof binds to the second epitope region.

The declaration filed on May 19, 2003, page 1, paragraph 3, states that example 4 teaches that the last 60 amino acids of the TSHR encoded by cDNA base pairs 1809-2295 was employed in the fusion protein because it represents a region of the TSHR that is almost entirely intracellular and as such is unlikely to interact with the TSHR autoantibodies. Such fact is contrary to the requirement of claim 77 part (a) that that THSR fragment has epitopes that are recognized by the autoantibodies.Therefore, the generated monoclonal antibodies would not bind to the same epitopes as the autoantibodies as required in the claims of the present invention.

Response to Arguments

The arguments filed on May 19, 2003 have been fully considered but they are not found persuasive.

The claims were previously rejected under 112, 1st paragraph for not enabled by the specification. The specification fails to teach two specific epitopes regions on the TSHR or TSHR fragment or how to generate antibodies that bind only one of the specific epitope regions. Applicants traverses this rejection because examples 1-5 on

pages 8-10 of the specification teaches how to produce an antibody that binds TSH receptor at the same time as TSH, indicating TSH receptor has at least two distinct epitope regions, with the antibody binding one region and TSH binding the other region.

Example 1 of the specification is teaching the preparation of cDNA clones for the full-length porcine TSH receptor. While the specification might be enable for the porcine TSH receptor and the method for cloning porcine TSH receptor, there is nowhere in the specification that discloses specific epitope regions on the TSH or TSH fragment or a method for generating antibodies that bind to a specific region on the TSHR or fragment.

Example 2 describes the preparation of a stable cell line for expressing the THS receptor. However, example 2 fails to teach the specific epitope regions on the TSHR or fragment or a method for generating antibodies that bind to a specific region on the TSHR or fragment.

Example 3 describes the preparation of detergent solubilized recombinant porcine TSH receptor expressed by a stable cell line prepared per the teaching of example 2. However, example 3 fails to teach the specific epitope regions on the TSHR or fragment or a method for generating antibodies that bind to a specific region on the TSHR or fragment.

Example 4 describes the preparation of a fusion protein. However, example 4 fails to teach the specific epitope regions on the TSHR or fragment or a method for generating antibodies that to bind a specific region on the TSHR or fragment.

Example 5 teaches immunization of BALB C mice with electroeluted TSH receptor/GST fusion protein until the titer of antibody was high. However, example 5 fails to teach the specific epitope regions on the TSHR or fragment or a method for generating antibodies that bind to a specific region on the TSHR or fragment.

Applicants also submit that Applicants have reproduced the referred examples 1-5 and have prepared a second antibody, Mab 8B7, in response to the recombinant fusion protein as taught by the examples. Applicants have further characterized the binding properties for Mab 8B7 and have found that Mab 8B7 binds to an epitope region of the TSH receptor distinct from an epitope region recognized by autoantibodies to the TSH receptor. Applicants also have enclosed a declaration by Dr. Bernard Rees Smith to substantiate the above, detailing the preparation and characterization of Mab 8B7.

Since examples 1-5 fail to teach the specific epitope regions on the TSHR or fragment or a method for generating antibodies that bind to a specific region on the TSHR or fragment, reproducing examples 1-5 would not satisfy the requirements of the specific epitope regions on the TSHR or fragment or a method of generating antibodies to a specific region on the TSHR or fragment.

Maintained Rejection(s)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention: - the instant invention is directed to a kit for detecting autoantibodies to thyroid stimulating hormone receptor (TSHR) or at least a TSHR fragment which kit comprises a source of TSHR or a TSHR fragment, said TSHR or TSHR fragment each having at least a first and second distinct epitope regions, wherein autoantibodies to said TSHR or TSHR fragment bind to the first epitope region but not said second epitope region; at least one antibody or fragment thereof, that binds to said second epitope region of the TSHR or TSHR fragment.

The state of the art: - the prior art fails to teach a kit comprising a TSHR or a TSHR fragment comprising two distinct epitope regions.

The predictability or lack thereof in the art:- in view of the lack of teachings in the prior art that show or suggests TSHR or TSHR fragment with two distinct epitopes

regions for binding to autoantibodies and antibody respectively, the level of predictability is low. The specification fails to teach specific epitope regions on the TSHR or TSHR fragment. Without the specific epitope regions, antibodies (which binds to the second epitope region) cannot be generated.

The amount of direction or guidance present: - the instant specification fails to provide guidance on how to generate antibodies that binds to the specific epitope region on the TSHR or TSHR fragment.

The presence or absence of working examples:- there is no examples in the specification that show generation of antibody which specifically binds to the second epitope region or specific epitope region to which autoantibodies would bind.

The quantity of experimentation necessary: - it would require an undue amount of experimentation for a skilled artisan to make and use the invention as claimed.

The relative skill of those in the art: The level of skill in the art is high.

The breadth of the claims:- the claimed kit is directed to a TSHR or TSHR fragment comprising two distinct epitope regions wherein autoantibodies bind to the first epitope region and at least one antibody or fragment thereof binds to the second epitope region.

The instant specification fails to describe specific epitope regions on the TSHR or TSHR fragment. Any four amino acid would constitute an epitope. However, in order to generate antibodies that bind to a specific region on the TSHR or fragment, such specific region has to be known. An undue amount of experimentation would be

required to identify any and all the possible epitopes found on the TSHR or fragment to enable the claimed kit.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 703-308-4398. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-746-5291 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Pensee T. Do
Patent Examiner
August 3, 2003

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
8/8/03